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(54) Title: ALKYLATED HEXAPEPTIDES

(57) Abstract

The present invention is directed to N^1-alkylated derivatives of desleucyl A82846B. These derivatives are useful as antibacterials and also as starting materials from which further antibacterial compounds are prepared.

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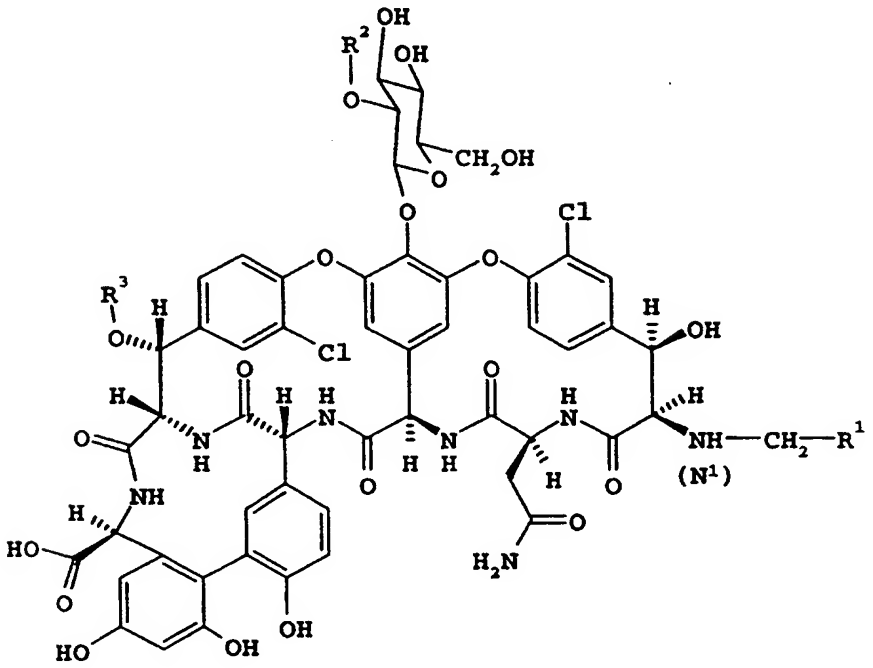
ALKYLATED HEXAPEPTIDES

The present invention is directed to glycopeptides and is directed in particular to derivatives of desleucyl-A82846B and its N^{DISACC} variations, also referred to as "hexapeptides" of A82846B. These derivatives are alkylated on the N^{1} amine of the hexapeptide. The derivatives are useful as antibacterials.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to alkylated A82846B hexapeptides of the formula



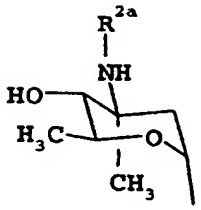
wherein R^1 represents

alkyl of C_1-C_{11},

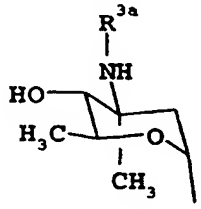
alkyl of C_1-C_{11}-R^{1a}, or

R^{1a}-(linker$_{(0\ or\ 1)}$-R^{1a})$_{0\ or\ 1}$,

wherein each R^{1a} is independently phenyl or phenyl substituted by one or two substituents, each of which is independently halo, hydroxy, loweralkyl of C_1-C_8, loweralkoxy of C_1-C_8, loweralkylthio of C_1-C_4, or trifluoromethyl, and "linker" is -O-, -CH_2-, or -O-$(CH_2)_n$- wherein n is 1-3; R^2 represents hydrogen or an epivancosaminyl radical of the formula

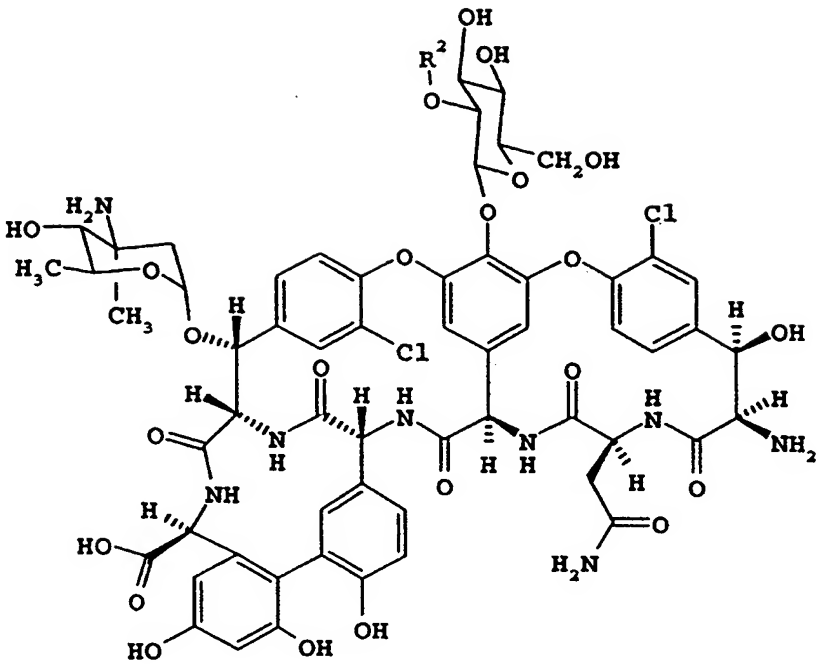


wherein R^{2a} represents hydrogen or $-CH_2-R^1$ wherein R^1 is defined as above and may be the same or different than the R^1 on the N^1 position; and wherein R^3 represents an epivancosaminyl radical of the formula



wherein R^{3a} is hydrogen, or, when R^2 is an epivancosaminyl and R^{2a} thereon is $-CH_2-R^1$, R^{3a} can also represent $-CH_2-R^1$ identical to that on the N^1-position; and the pharmaceutically acceptable salts thereof.

The alkylated A82846B hexapeptides of the present invention are in general prepared by reductive alkylation of the corresponding A82846B hexapeptides of the formula:



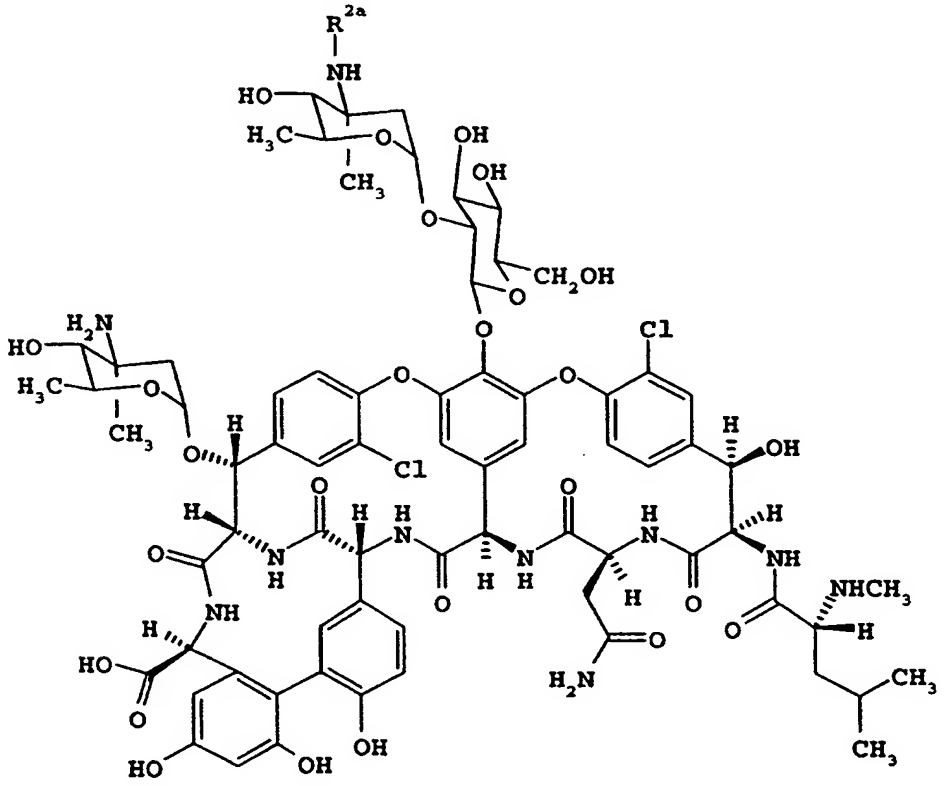
wherein R^2 is as defined above. In carrying out the reductive alkylation, the A82846B hexapeptide is first reacted with an aldehyde of the formula R^1-CHO, wherein R^1 is as defined above. This results in the formation of a Schiff's base, which is thereafter reduced to obtain the desired alkylated A82846B hexapeptide. Both reaction steps are carried out in a polar solvent, such as DMF, methanol, or a mixture of the same, and at temperatures of from 25° to 100°C, preferably 60° to 70°C. Preferred reducing agents are sodium borohydride and especially sodium cyanoborohydride.

In a further embodiment, the hexapeptide, aldehyde, and reducing agent, especially sodium cyanoborohydride, are all mixed together at one time. This embodiment is preferred for the reaction with nonbenzylic aldehydes, but may be used as well for the reaction with benzylic aldehydes.

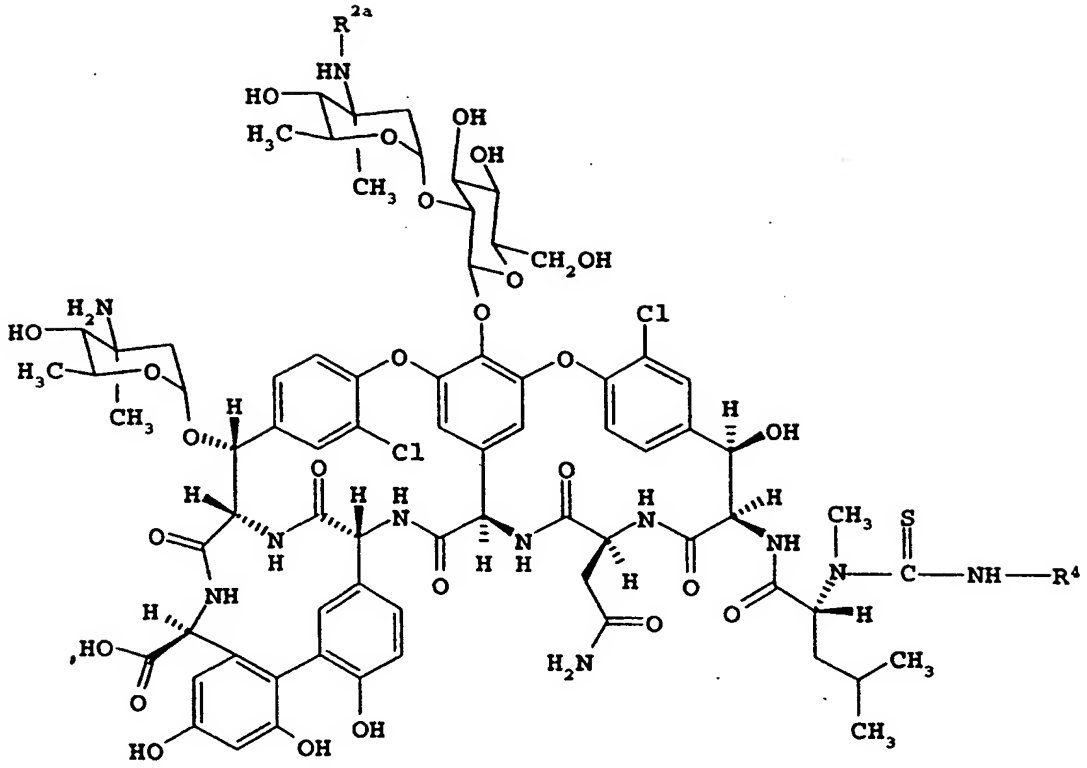
Reductive alkylation of the A82846B hexapeptide can result in alkylation of more than one site. The N^1-position reacts preferentially, but alkylation may also occur at the

N^{DISACC} and/or $N^{MONOSACC}$ sites in the molecule. Different alkyl groups on the N^{1}-position and the N^{DISACC} location are conveniently achieved by starting with an A82846B hexapeptide with the desired N^{DISACC} group already present, and thereafter alkylating the N^{1}-position.

The starting A82846B hexapeptides are themselves synthesized from the parent glycopeptides:



wherein R^{2a} is as defined above. This synthesis is by the "Edman degradation", a two-step process for the cleavage of the N-terminal residue of a peptide or protein. In the present invention, the above parent glycopeptide is first reacted with an isothiocyanate of the formula SCN-R^{4}, to obtain an intermediate N^{LEU}-(thiocarbamoyl)-A82846B compound of the formula



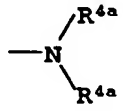
In the foregoing formula, R^4 represents

alkyl of C_1-C_{10},

phenyl,

naphthyl, or

phenyl substituted by one or two substituents, each of which is independently halo, loweralkyl of C_1-C_4, loweralkoxy of C_1-C_4, benzyloxy, nitro, or



wherein each R^{4a} is independently loweralkyl of C_1-C_4.

This reaction is conveniently carried out in water with pyridine, at a temperature of 25°-30°C, employing a slight

excess of the isothiocyanate reactant. The N^{LEU}-(thiocarbamoyl)A82846B intermediate can be separated in conventional manner or can be employed after removal of reaction solvent in the second step of the Edman degradation.

In the second step, the N^{LEU}-(thiocarbamoyl)A82846B is reacted with an organic acid, preferably trifluoroacetic acid, in a non-polar solvent such a dichloromethane. The reaction proceeds at temperatures of from 0°C to 35°C but is preferably carried out at temperatures of from 0°C to 25°C. The reaction is generally complete in several hours. The resulting hexapeptide product is separated and purified if desired in conventional procedures.

The second step of the Edman degradation can in some instances result in loss of the disaccharide epivancosamine. Longer reaction times can be used to obtain the N^{DISACC}-des-epivancosaminyl compound (R^2=hydrogen).

The compounds of the present invention readily form salts, which can be prepared in conventional manner.

The following examples illustrate the preparation of the compounds of the present invention.

Preparation of N^{LEU}-(phenylthiocarbamoyl)-N^{DISACC}-(p-(p-chlorophenyl)benzyl)A82846B

N^{DISACC}-(p-(p-Chlorophenyl)benzyl)A82846B trihydrochloride (100.0 mg, 0.0526 mmol) was dissolved in 10 ml H_2O - pyridine (1:1 v/v) and treated with phenyl isothiocyanate (0.010 ml, 0.083 mmol). The resulting mixture was stirred at room temperature for 1 hr at which time HPLC analysis indicated complete consumption of the starting material. The reaction mixture was concentrated *in vacuo* and the crude product was purified by preparative HPLC

to give 76.6 mg (76% yield) of the title compound. FAB-MS: calc. for $C_{93}H_{102}Cl_3N_{11}O_{26}S$ 1925.5, obtained 1928.5 (M+3).

Preparation of N^{DISACC}-(p-(p-chlorophenyl)benzyl)-desleucyl-A82846B from isolated thiourea

A sample of the purified N^{LEU}-(phenylthiocarbamoyl)-N^{DISACC}-(p-(p-chlorophenyl)benzyl)A82846B (63.3 mg, 0.0327 mmol) was suspended in 10 ml CH_2Cl_2, cooled to 0 °C, then treated with trifluoroacetic acid (0.10 ml). After 1 hr the reaction mixture was warmed to room temperature and stirred an additional 2 hr. The solvent was removed *in vacuo* and the crude product was purified by preparative HPLC to give 25.3 mg (46% yield) of the title compound as a white powder. FAB-MS: calc. for $C_{79}H_{84}Cl_3N_9O_{25}$ 1663.5, obtained 1666.4 (M+3).

Preparation of N^{DISACC}-(p-phenylbenzyl)desleucyl-A82846B without isolation of thiourea intermediate

N^{DISACC}-(p-Phenylbenzyl)A82846B (41.0 mg, 0.0233 mmol) was dissolved in 4 ml H_2O - pyridine (1:1 v/v) and treated with phenyl isothiocyanate (0.0040 ml, 0.033 mmol). The resulting mixture was stirred at room temperature for 3 hr at which time HPLC analysis indicated complete consumption of the starting material. The reaction mixture was concentrated *in vacuo* to give the crude thiourea intermediate as a white solid. The thiourea derivative was then suspended in 10 ml CH_2Cl_2, cooled to 0 °C, then treated with trifluoroacetic acid (0.25 ml). After 30 minutes the reaction mixture was warmed to room temperature and stirred an additional 1 hr. The solvent was removed *in vacuo* and the crude product was purified by preparative HPLC to give 14.0 mg (37% yield) of the title compound as a white powder. FAB-MS: calc. for $C_{79}H_{85}Cl_2N_9O_{25}$ 1629.5, obtained 1632.5 (M+3).

Preparation of Example 19

A sample of purified desleucyl-A82846B (141 mg, 0.0962 mmol), 8-phenyloctanal (28 mg, 0.137 mmol), and sodium cyanoborohydride (35 mg, 0.556 mmol) were dissolved in 20 ml DMF-MeOH (1:1 v/v). The resulting mixture was heated to 65°C and stirred for 1 hour at which time HPLC analysis revealed complete consumption of the starting material. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, and the crude product purified by preparative HPLC to give 20 mg (13% yield) of Example 19.

Preparation of Example 3

A sample of purified desleucyl-A82846B (140 mg, 0.0956 mmol) and 4-phenylbenzaldehyde (30 mg, 0.165 mmol) was dissolved in 20 ml DMF-MeOH (1:1 v/v). The resulting mixture was heated to 65 °C and stirred for 1.5 hours, sodium cyanoborohydride (27 mg, 0.429 mmol) was added and the reaction stirred for an additional 1.5 hours at which time HPLC analysis revealed consumption of the starting material. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, and the crude product purified by preparative HPLC to give 38 mg (24% yield) of Example 3.

The HPLC procedures reported in these examples were as follows:

Analytical: Reactions were monitored by analytical HPLC using a Waters C_{18} μBondapak or Novapak C_{18} column (3.9x300 mm) and UV detection at 280 nm. Elution was accomplished with a linear gradient of 5% CH_3CN - 95% buffer to 80% CH_3CN - 20% buffer over 30 minutes. The buffer used was 0.5% triethylamine in water, adjusted to pH 3 with H_3PO_4.

Preparative: Crude reaction mixtures were purified by preparative HPLC using a Waters C_{18} Nova-Pak column (40x300 mm) and UV detection at 280 nm. Elution was accomplished with a linear gradient of 5% CH_3CN - 95% buffer to 80% CH_3CN - 20% buffer over 30 minutes. The buffer used was 0.5% triethylamine in water, adjusted to pH 3 with H_3PO_4. The desired fractions were subsequently desalted with a Waters C_{18} Sep-Pak (35 cc) followed by lyophilization.

Compounds were desalted as follows. A Waters Sep-Pak cartridge was pre-wet with methanol (2-3 column volumes) then conditioned with water (2-3 column volumes). The sample, dissolved in a minimum volume of water, was loaded onto the Sep-Pak column which was then washed with water (2-3 column volumes) to remove the unwanted salts. The product was then eluted with an appropriate solvent system, typically 1:1 CH_3CN/H_2O, CH_3CN, and/or methanol. The organic solvent component was removed *in vacuo* and the resulting aqueous solution lyophilized to give the final product.

Representative compounds of the present invention are listed in the following table:

TABLE I

EX #	NAME	FAB-MS	M + X	Analytical HPLC*, min
1	N^1-(12-PHENYL-n-DODECYL)DESLEUCYL-A82846B	1710.5	3	21.1
2	N^1-(12-PHENYL-n-DODECYL)-N^{DISACC}-(p-PHENYLBENZYL)-DESLEUCYL-A82846B	1876.1	2	22.9
3	N^1-(p-PHENYLBENZYL)-DESLEUCYL-A82846B	1632.5	3	14.1
4	N^1, N^{DISACC}-BIS(p-PHENYLBENZYL)-DESLEUCYL-A82846B	1798.4	3	17.4
5	N^1-BENZYL-N^{DISACC}-(p-PHENYLBENZYL)-DESLEUCYL-A82846B	1722.7	3	14.9
6	N^1, $N^{MONOSACC}$-DIBENZYL-N^{DISACC}-(p-PHENYLBENZYL)-DESLEUCYL-A82846B	1812.9	3	16.5
7	N^1, N^{DISACC}-DIHEXYLDESLEUCYL-A82846B	1633	1	14.2
8	N^1, N^{DISACC}, $N^{MONOSACC}$-TRI-n-HEXYLDESLEUCYL-A82846B	1718.2	3	16.7
9	N^1, N^{DISACC}-BIS(p-HYDROXYBENZYL)-DESLEUCYL-A82846B	1679.1	4	9.9
10	N^1-n-HEXYLDESLEUCYL-A82846B	1549.6	2	11.8
11	N^1-n-HEXYL-N^{DISACC}-(p-PHENYLBENZYL)-DESLEUCYL-A82846B	1716.8	3	16.2
12	N^1-BENZYLDESLEUCYL-A82846B	1556.3	3	10.1
13	N^1-(p-HYDROXYBENZYL)-DESLEUCYL-A82846B	1572.1	3	9.0
14	N^1-(6-PHENYL-n-HEXYL)DESLEUCYL-A82846B	1626.1	3	15.5
15	N^1, N^{DISACC}-BIS(6-PHENYL-n-HEXYL)-	1785.4	2	19.1

	DESLEUCYL-A82846B			
16	N^1, N^{DISACC}-BIS(10-PHENYL-n-DECYL)-DESLEUCYL-A82846B	1898.7	3	24.5
17	N^1-(p-HYDROXYBENZYL)-N^{DISACC}-(p-PHENYLBENZYL)-DESLEUCYL-A82846B	1737.3	2	14.1
18	N^1-(10-PHENYL-n-DECYL)DESLEUCYL-A82846B	1682.6	3	19.7
19	N^1-(8-PHENYL-n-OCTYL)DESLEUCYL-A82846B	1653.6	2	17.6
20	N^1-(6-PHENYL-n-HEXYL)-N^{DISACC}-(p-PHENYLBENZYL)-DESLEUCYL-A82846B	1792.5	3	18.4
21	N^1-(p-(3-PHENYL-n-PROPOXY)BENZYL)DESLEUCYL-A82846B	1690.3	3	15.9
22	N^1-(p-(3,5-BIS-(TRIFLUOROMETHYL)-PHENYL)BENZYL)-DESLEUCYL-A82846B	1768.2	3	17.5
23	N^1-(p-(n-OCTYLOXY)-BENZYL)DESLEUCYL-A82846B	1683.5	2	18.3
24	N^1-(p-(METHYLTHIO)-BENZYL)DESLEUCYL-A82846B	1602.1	3	13.6
25	N^1, N^{DISACC}-BIS(p-(METHYLTHIO)-BENZYL)DESLEUCYL-A82846B	1738.1	3	11.3
26	N^1-(p-(3,5-BIS-(TRIFLUOROMETHYL)-PHENYL)BENZYL)-N^{DISACC}-(p-PHENYLBENZYL)-DESLEUCYL-A82846B	1934.6	3	19.4
27	N^1-(p-(3,5-BIS-(TRIFLUOROMETHYL)-PHENYL)BENZYL)-N^{DISACC}-(p-(p-CHLOROPHENYL)BENZYL-	1968.5	3	21.2

28	DESLEUCYL-A82846B N^1-(6-PHENYL-n-HEXYL)-N^{DISACC}-(p-(p-CHLOROPHENYL)BENZYL) DESLEUCYL-A82846B	1826.6	3	19.3

*Waters C_{18} μBondapak

The compounds of the present invention are useful for the treatment of bacterial infections. Therefore, in another embodiment, the present invention is directed to a method for controlling a bacterial infection in a host animal, typically a warm-blooded animal, which comprises administering to the host animal an effective, antibacterial amount of a compound of the present invention. In this embodiment, the compounds can be used to control and treat infections due to various bacteria, but especially gram-positive bacteria. In a preferred embodiment, the compounds are used to control and treat infections due to bacteria resistant to existing antibacterials. For example, certain bacteria are resistant to methicillin, and yet others are resistant to vancomycin and/or teicoplanin. The present compounds provide a technique for controlling and treating infections due to such resistant bacterial species.

In carrying out this embodiment of the invention, the compounds of the present invention can be administered by any of the conventional techniques, including the oral route and parenteral routes such as intravenous and intramuscular. The amount of compound to be employed is not critical and will vary depending on the particular compound employed, the route of administration, the severity of the infection, the interval between dosings, and other factors known to those skilled in the art. In general, a dose of from about 0.5 to about 100 mg/kg will be effective; and in many situations, lesser doses of from about 0.5 to about 50 mg/kg will be effective. A compound of the present invention can be

administered in a single dose, but in the known manner of antibacterial therapy, a compound of the present invention is typically administered repeatedly over a period of time, such as a matter of days or weeks, to ensure control of the bacterial infection.

Also in accordance with known antibacterial therapy, a compound of the present invention is typically formulated for convenient delivery of the requisite dose. Therefore, in another embodiment, the present invention is directed to a pharmaceutical formulation comprising a compound of the present invention, in combination with a pharmaceutically-acceptable carrier. Such carriers are well known for both oral and parenteral routes of delivery. In general, a formulation will comprise a compound of the present invention in a concentration of from about 0.1 to about 90% by weight, and often from about 1.0 to about 3%.

The antibacterial efficacy of the present compounds is illustrated by Table II. The minimal inhibitory concentrations (MICs) were determined using a standard broth micro-dilution assay.

TABLE II: Antibacterial Activity, Minimal Inhibitory Concentration (MIC) against Various Organisms*

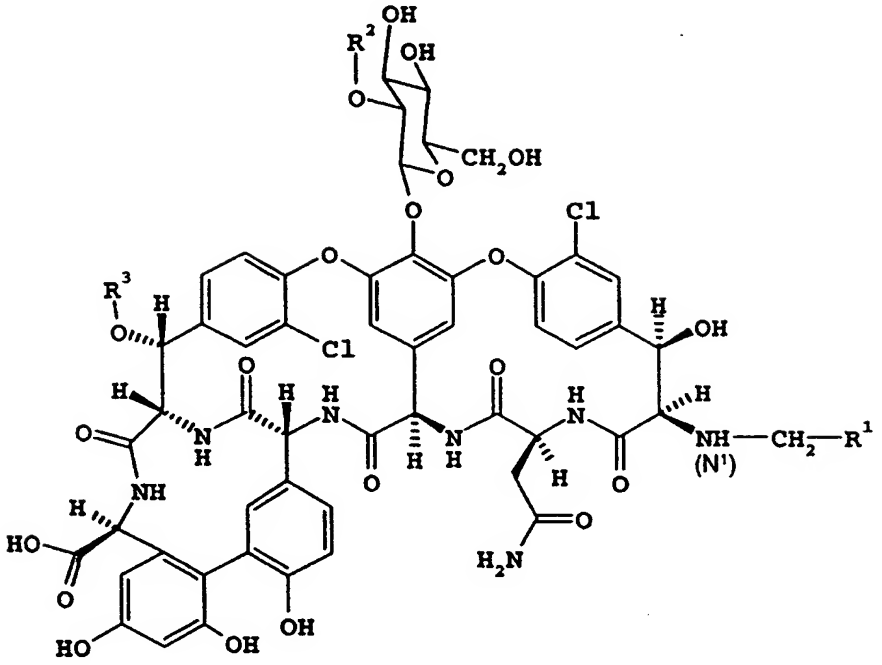
EX #	RESISTANT	SENSITIVE	SA 446	SA 489	SA 447	SH 105	SH 415	SE 270	SPY C203	SPN P1
1	13	9.2	8	2	2	4	8	4	0.125	NO GROWTH
2	45	24	32	64	>64	>64	>64	32	4	≤.06
3	>128	21	8	8	8	8	16	8	≤.06	≤.06
4	53	21	4	2	2	2	2	2	≤.06	≤.06
5	23	9.2	2	2	2	2	2	2	0.125	0.5
6	16	6.1	2	2	2	0.5	1	0.5	0.125	0.5
7	>128	111	16	8	8	4	8	16	8	8
8	76	55	16	8	8	4	16	8	1	2
9	>128	>128	16	16	16	32	32	32	16	32
10	>128	>128	32	16	32	64	64	32	16	32
11	27	11	1	1	0.5	2	1	0.5	0.125	0.125
12	>128	128	>64	64	>64	>64	>64	>64	2	2
13	54	4	16	8	32	>64	>64	32	0.25	≤.06
14	>50	37	16	8	8	8	8	8	≤.06	≤.06
15	8	6	4	2	2	1	2	2	0.125	0.5
16	>128	>11	>64	64	>64	>64	>64	>64	8	16
17	27	2.6	1	1	0.5	0.5	1	0.5	≤.06	≤.06
18	19	12	2	2	2	4	2	4	0.25	0.5
19	45	25	2	1	1	2	2	4	0.5	0.5
20	64	11	4	4	4	1	1	1	≤.06	≤.06
21	>128	32	4	4	4	4	8	4	≤.06	≤.06
22	9.5	4.6	2	1	2	1	2	2	≤.06	≤.06
23	11	9.2	8	4	4	4	8	4	0.25	1
24	>128	>128	32	16	32	32	64	32	8	8
25	6.7	2.6	8	4	4	4	8	8	4	1
26	5.7	6.1	8	4	4	2	4	4	0.25	≤.06
27	9.5	6.1	64	32	32	8	32	8	64	32
28	6.7	7	8	8	8	4	2	4	4	16

*

ABBREVIATIONS	ORGANISM
RESISTANT	*Enterococcus faecium* and *faecalis* (geometric mean of 4-6 isolates)
SENSITIVE	*Enterococcus faecium* and *faecalis* (geometric mean of 4-6 isolates)
SA446	*Staphylococcus aureus* 446
SA489	*Staphylococcus aureus* 489
SA447	*Staphylococcus aureus* 447
SH 105	*Staphylococcus haemolyticus* 105
SH 415	*Staphylococcus haemolyticus* 415
SE 270	*Staphylococcus epidermidis* 270
SPY C203	*Streptococcus pyogenes* C203
SPN P1	*Streptococcus pneumoniae* P1

WE CLAIM:

1. A compound of the formula



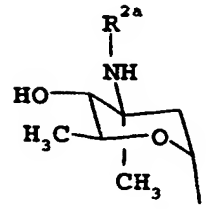
wherein R^1 represents

alkyl of C_1-C_{11},

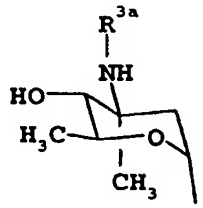
alkyl of C_1-C_{11}-R^{1a}, or

R^{1a}-(linker$_{(0\ or\ 1)}$-R^{1a})$_{0\ or\ 1}$,

wherein each R^{1a} is independently phenyl or phenyl substituted by one or two substituents, each of which is independently halo, hydroxy, loweralkyl of C_1-C_8, loweralkoxy of C_1-C_8, loweralkylthio of C_1-C_4, or trifluoromethyl, and "linker" is -O-, -CH_2-, or -O-$(CH_2)_n$- wherein n is 1-3; R^2 represents hydrogen or an epivancosaminyl radical of the formula



wherein R^{2a} represents hydrogen or $-CH_2-R^1$ wherein R^1 is defined as above and may be the same or different than the R^1 on the N^1 position; and wherein R^3 represents an epivancosaminyl radical of the formula



wherein R^{3a} is hydrogen, or, when R^2 is an epivancosaminyl and R^{2a} thereon is $-CH_2-R^1$, R^{3a} can also represent $-CH_2-R^1$ identical to that on the N^1-position; or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 in which R^1 is $R^{1a}-(\text{linker}_{(0 \text{ or } 1)}-R^{1a})_{0 \text{ or } 1}$ as defined.

3. A compound of Claim 1 in which R^2 is an epivancosaminyl radical wherein R^{2a} represents $-CH_2-R^1$.

4. A compound of Claim 3 in which R^{2a} is p-phenylbenzyl.

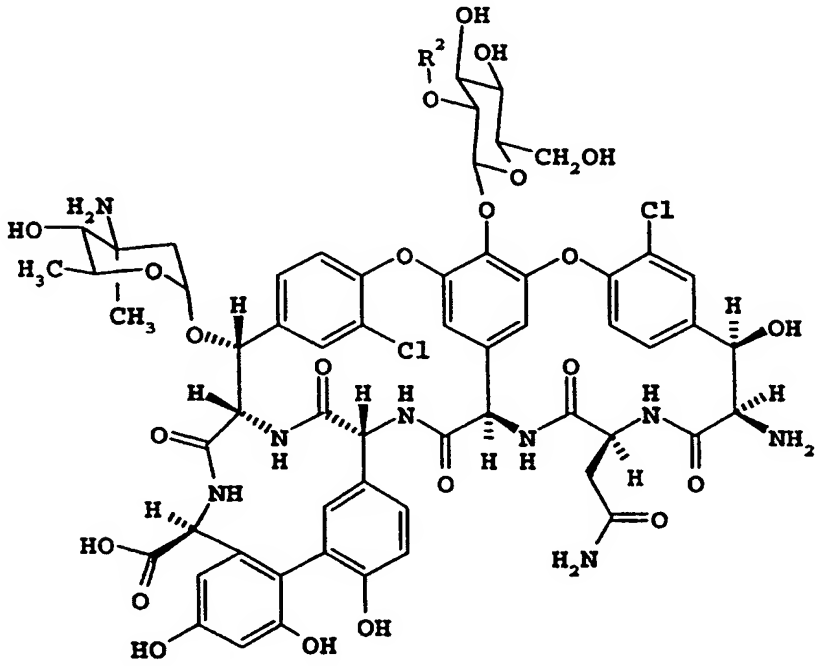
5. A compound of Claim 3 in which R^{2a} is p-(p-chlorophenyl)benzyl.

6. A pharmaceutical formulation comprising a compound of Claims 1 in combination with a pharmaceutically-acceptable diluent or carrier.

7. A method of treating a bacterial infection in a host comprising the step of administering to the host an effective amount of a formulation of Claim 6.

8. A method of Claim 7 wherein the bacterial infection is attributable to a vancomycin-resistant-enterococcus.

9. A process for the preparation of a compound as claimed in Claim 1 which comprises reductively alkylating a parent glycopeptide of the formula



wherein R^2 is as defined in Claim 1, with an aldehyde of the formula R^1CHO, wherein R^1 is as defined in Claim 1, and if desired, thereafter forming a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/08986

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 37/02; C07K 7/50 , 9/00
US CL :530/317, 322; 514/8, 9
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/317, 322; 514/8, 9

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PAVLOV, A.Y. et al. Modification of Glycopeptide Antibiotic Eremomycin by the Action of Alkyl Halides And Study on Antibacterial Activity of the Compounds Obtained. The Journal of Antibiotics. February 1994, Vol. 47, No. 2, pages 225-231.	1-10
Y	NICAS, T.I. et al. Activity of Glycopeptides against Vancomycin-Resistant Gram-Positive Bacteria. Antimicrobial agents and chemotherapy. September 1989, Vol. 33, No. 9, pages 1477-1481.	1-10
Y	NAJARAJAN et al. Synthesis and Antibacterial evaluation of N-Alkyl Vancomycins. January 1989, Vol. 62, No. 1, pages 63-72.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 03 JUNE 1998	Date of mailing of the international search report 14 JUL 1998
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